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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/786,907	BOGEN ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2010 and 30 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37,77,83-94,97-108,119,121 and 123* is/are pending in the application.

4a) Of the above claim(s) *1-37,77,84-87,93,94,97 and 101-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83,88-92,96-100,119,121 and 123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/26/10 and 11/30/10 has been entered.

2. Claims 1-37, 77, 83-94, 97-108, 119, 121 and 123 are all the pending claims for this application.

3. Claims 1-37, 77, 84-87, 93, 94, 97, 101-108 are withdrawn from examination.

4. Claims 83, 88-92, 98-100, 119, 121 and 123 are all the pending claims under examination with targeting units for a ligand species of soluble CD40 ligand and the chemokines, RANTES and MIP-1α, and the species of antigenic units for an antigenic scFv.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. The rejection of Claims 83, 88-92, 98-100, 119, 121 and 123 under 35 U.S.C. 103(a) as being unpatentable over by Herman (US 20050069549; published March 31, 2005; filed Jan 14, 2003; cited in the PTO 892 form of 11/7/06) in view of Slavin-Chiorini et al. (Int. J. Can. 53:97-103 (1993)) is maintained.

The rejection was set forth in the Office Action of 10/30/09 as follows:

"Claims 83, 88-92, 98-100, 119 and 121-123 are interpreted as being drawn to an isolated nucleic acid encoding a monomer unit of a recombinant antibody-based dimeric molecule, said nucleic acid encoding an antigenic unit, a dimerization motif and a targeting unit operably connected to encode said monomer unit, and wherein said antibody-based dimeric molecule comprises two of said monomer units connected through said dimerization motif, said dimerization motif comprising an Ig hinge region and a Cy3 domain of each monomer unit, wherein each Ig hinge region contributes to dimerization via disulfide bridging to the other Ig hinge region and each Cy3 domain contributes to dimerization via hydrophobic interactions to the other Cy3 domain, and wherein each of said monomer unit comprises a targeting unit for an antigen presenting cell and an antigenic unit, wherein said targeting unit and said antigenic unit in the monomer unit are separated by said dimerization motif and wherein said monomer units each lack a CH2 domain (Claim 83), wherein at least one of said targeting unit is a ligand (Claim 88), and wherein said ligand is soluble CD40 ligand or a chemokine (Claim 89), wherein said ligand is a chemokine (Claim 90), wherein said chemokine is RANTES or Macrophage Inflammatory Protein 1 alpha (Claim 91), wherein said chemokine is MIP-Ia (Claim 92), wherein said targeting unit have the ability to target a chemokine receptor (Claim 98), wherein at least one of said antigenic unit is an antigenic scFv (Claim 99), wherein said antigenic scFv has VL and VH chains from a monoclonal Ig produced by myeloma or lymphoma (Claim 100).

Claim 119 is drawn to a vector comprising the nucleic acid according to claim 83. Claim 121 is drawn to a composition comprising a nucleic acid according to claim 83 or a vector comprising the nucleic acid according to claim 83, in combination with a physiologically acceptable diluent or carrier. Claim 122 is drawn to a composition comprising a cell of the cell line according to claim 120, in combination with a physiologically acceptable diluent or carrier.

Claim 123 is drawn to a kit for preparation of a recombinant antibody- based molecule encoded by the nucleic acid according to claim 83, the kit comprising a nucleic acid according to claim 83.

The nucleic acid encoding a monomer comprising the (targeting unit – dimerization motif (Ig hinge *and* Cγ3)-antigenic unit) or (antigenic unit- dimerization motif (Ig hinge *and* Cγ3)- targeting unit) was prima facie obvious at the time of the invention over Herman and Slavin-Chiorini.

Herman discloses nucleic acids, vectors comprising nucleic acids and vector transfected cell lines encoding a multispecific ligand comprising at least two different binding specificities for different target ligands comprising any combination of one or more antibody fragments or recombinant reconstructions (scFvs) of antibodies including tetraspecific antibody formats and fusions of the antibody to other functional moieties (eg. toxins, cytokines, chemokines, streptavidin, adhesion molecules) [0107-0108], where the multispecific ligand comprises an Fc portion and an Ig hinge portion. An Fc portion may be a partial Fc portion (eg. minibody-CH3) [0069]. The amino acid composition (including length) of the hinge portion should provide means for linking two typically heavy chains, eg. through one or more disulfide bonds, leucine zipper, fos-jun, optionally a flexible hinge typical of an IgG1 or having one to several more disulfide bonds eg. IgG3) [0116]. The binding characteristics of the multispecific ligand e.g., scfv, is that the target ligand is of sufficient affinity to effectively bind or remain bound without the other unit being available for simultaneous binding [0119]. An example of one monomer comprises a first ligand moiety which recognizes a first target ligand that is over-expressed on a disease associated entity (for example a diseased or disease-causing or mediating cell or infectious agent) and a second ligand binding moiety that recognizes a target ligand and wherein the first target ligand is characterized in that it does not lend itself to facilitating or permitting internalization of the second ligand binding moiety [0122].

Herman discloses the heterofunctional ligand is fused or conjugated to a therapeutic agent or a moiety that binds to a ligand which effects binding to another immune cell, for example a T cell or APC. The multispecific ligand is a tetraspecific antibody or the first moiety binds to but is incapable of modulating the activity of an immune cell and the second moiety modulates the activity of the immune cell independently of the first moiety [0137].

Herman discloses a multispecific ligand which comprises a first ligand binding moiety which neutralizes a ligand eg. a natural ligand such as a chemokine and a second ligand binding moiety which binds to a cell marker associated with a cell [0138]. Examples of proteins which are targeted by multispecific ligand (targeting unit) include CD40 [0164], MIP-1 alpha and RANTES [0428]. Herman discloses a multispecific ligand comprising an anti-idiotype antibody (antigenic unit) so as to facilitate a desired immune response eg. vaccination type responses [0172, 0252]. For one embodiment, Herman discloses a multispecific ligand containing an immunocytokine containing an anti-idiotypic antibody component and a cytokine component [0018]. Herman discloses nucleic acids, expression vectors and host cells expressing the vectors to produce a multispecific ligand [0241- 0298; 0314-0319]. Herman discloses a kit comprising one or more polynucleotides comprising one or more DNA sequences, where the DNA sequences encode one or more polypeptides which are sufficient to constitute a multispecific ligand as defined in any of the preceding paragraphs [0424]. Herman discloses the element of CH2 domain being optional and the element of CH3 domain being optional whereas Slavin-Chiorini discloses deleting the CH2 domain altogether and maintaining a CH3 constant domain for an Ig molecule.

Slavin-Chiorini discloses the long-felt need to obtain recombinant Ig molecules with rapid plasma clearance and little or no ability to elicit a HAMA response for use in diagnostic or therapeutic regimens, and that by deleting the CH2 domain of an intact Mab, the ordinary artisan could reasonably expect to obtain these results for murine and chimeric antibodies (p. 97, Col. 1, ¶1 and 3). The Ig molecule is shown in Figure 1 comprising a CH2 constant region deletion, an intact hinge region with a linker peptide bridging the CH1 and CH3 constant domains. Slavin-Chiorini discloses there is a reduction in disulfide bond formation between the heavy chains for the CH2 domain deletion, but that presence of the peptide linker may contribute to the stability of the Ig molecule. Slavin-Chiorini discloses that these alternative forms of Ig molecules demonstrate faster clearance rate, more rapid tumor targeting and lack of metabolic uptake in normal tissues which provide advantages over the full molecules.

The ordinary artisan would have been motivated and assured of success in having produced a nucleic acid encoding a monomer comprising the (targeting unit – dimerization motif (Ig hinge *and* $C\gamma3$)- antigenic unit) or (antigenic unit- dimerization motif (Ig hinge *and* $C\gamma3$)- targeting unit) based on the combined disclosures of Herman and Slavin-Chiorini. Herman teaches all of the elements for designing such a construct, for example, fusion proteins comprising a immunocytokine having an anti-idiotypic antibody component and a cytokine component fused therewith or conjugated thereto, or ligands including bispecific antibodies, antibody fusions/ conjugates eg. where the immune affecting antibody portion or other moiety is conjugated, fused etc. to an antibody or fragment that binds to an entity associated marker [0223]. Herman teaches making a "divalent immunoconjugate" by attaching therapeutic agents to a carbohydrate moiety and to a free sulfhydryl group [0338]. Accordingly, Herman teaches an example of a bispecific antibody comprising two dAb components comprising linked via a linker having at least part of a constant region for fusion for example to a toxin (eg. at least a partial hinge region, and preferably also at least a partial CH2 domain (optionally also at least a partial CH3 domain) [0345]. Herman requires the hinge region, does not necessarily require the CH2 domain although preferable, and may include the CH3 domain, which is considered to read on the constructs in view of all of the other elements taught (and discussed above) by Herman as possible combinations for constructs. The ordinary artisan would have been motivated to have deleted the CH2 domain entirely from the construct of Herman where it was well known according to Slavin-Chiorini at the time of the invention, that the CH2 domain contains many of the effector functions for the constant region of an Ig and the sole N-linked glycosyaltion site in human $C\gamma1$. Eliminating the CH2 domain would renders the Ig into a less complex molecule in terms of

reduced immunogenicity, increased target specificity and rapid clearance from circulation. Maintaining the a linker and CH3 domain according to Slavin-Chiorini at the time of the invention would stabilize the expressed molecular complex with respect to binding (It is not a requirement that the Examiner establish that the cited art contains all the elements of the rejected claim, as the analysis under 35 U.S.C. § 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR, 550 U.S. at 418.).

The ordinary artisan would have been assured of reasonably success in having produced the nucleic acid where each of the reference taught the reagents and steps for making recombinant Ig-like molecules with bi-specific binding properties, to maximize the stability of an expressed protein monomer in pairwise formation via a linker and CH3 domain, and to reduce non-specific biological effects for an Ig-like molecule by deleting the CH2 domain. For all of these reasons, the claims were prima facie obvious at the time of the invention."

The rejection was maintained in the Office Action of 6/1/10 as follows:

"Applicants allegations on pp. 13-19 of the Response of 3/1/10 have been considered and are not found persuasive.

a) Applicants allege the encoded constructs according to the present claims *need not include an antigen binding site of an antibody*. Rather, the important functionalities of the two units (the antigenic unit and the targeting unit) are their ability to function as an antigen (which can induce antibodies) and to target the homodimeric molecule to a relevant cell (for instance an antigen presenting cell). The homodimeric molecules are useful as vaccine agents, and this is also the case for the claimed nucleic acids (when used in nucleic acid vaccination) but the nucleic acids may also be used in expression vectors for recombinant production of the homodimeric molecules.

Response to Arguments

Unless the examiner is in need of new prescription eye glass lenses, then it is not understand how Applicants attorney can read the required limitation out of the claims, i.e., the targeting unit is an antibody-based molecule (e.g., a scfv) (see Claims 84-87). In addition, it is not understand how Applicants attorney can read the required limitation out of the claims, i.e., the antigenic unit is an antibody-based molecule (e.g., a scfv) (see Claims 99 and 100). Applicants' attorney would have the Office believe that the claims are distinguishable over Herman and Slavin-Chiorini because they do not require an antigen binding site of an antibody, when the instant pending claims specifically make this a requirement of the construct irrespective of whether the molecule is a vaccine. When the invention is taken as whole, then a given species of construct could conceivably comprise two antibody-based antigen binding units, one for the targeting unit and the other for the antigenic unit.

b) Applicants allege "Herman... does not enable nucleic acids encoding any and all multispecific constructs. In particular, Herman does not at all address production of antibody-based dimeric molecules comprising two monomer units encoded by the same nucleic acid...."

Response to Arguments

MPEP 2144.02 states in part: "In certain< circumstances >where appropriate<, ** an examiner *>may< take official notice of facts not in the record..., however such rejections should be judiciously applied." Here the examiner submits that Applicants attorney statement of facts asserted to be well-known, or to be common knowledge in the art are not capable of instant and unquestionable demonstration as being well-known. Accordingly, Applicants are requested to supply documentary evidence to support the conclusion that the ordinary artisan would not be enabled to express two monomer units from the same nucleic acid as alleged by Applicants attorney.

c) Applicants allege "A rapid plasma clearance rate (as taught by Slavin-Chiorini) is exactly the opposite of what is aimed at in the *present claims* and specification, wherein a prolonged serum half-life (i.e., slow plasma clearance) of the antibody-like expression products is desired..."

Response to Arguments

The examiner resubmits that the discussion in the rejection as regards Slavin-Chiorini deleting CH2 domains in order to achieve a rapid clearance was to set forth grounds for a prima facie motivation to delete the CH2 domain. Notably, Applicants have ignored the second grounds for motivation to delete the CH2 domain discussed in Slavin-Chiorini, which was to reduce the HAMA. Instead, Applicants conduct a lengthy and quite irrelevant discourse on why prolonged serum half life is better than rapid clearance and further urge the Office to believe that prolonged serum half life is inherent to their instant claimed invention. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., prolonged serum half-life) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants allegations on pp. 12-17 of the Response of 10/26/10 and the 1.132 Declaration of Dr. Sally Ward Ober filed with the Response of 10/26/10 have been considered and not found persuasive. Applicants and the Declarant allege the two cited reference do not provide the motivation to modify the constructs of the respective disclosures to obtain the instant claimed construct because Herman teaches prolonging the serum half-life of the multispecific ligand, whereas, Slavin-Chiorini teaches reduces the plasma half-life for Mabs.

Response to Arguments

The examiner submits that the properties of antibody serum/blood clearance and antibody half-life are all separately defined parameters commonly used in drug studies. See the attached on-line dictionary definitions for each phrase:

Antibody half-life: mean survival time for antibody molecules;

Clearance: rate of removal from blood.

Finally, the examiner submits that Herman is not limited as only teaching prolonging "serum half-life" for the antibody construct where Herman teaches examples of "half-life":

"Methods of prolonging the half-life of antibodies, producing bispecifics, scfvs and dsFvs and altering Fc effector function are well known and noteworthy references include U.S. Pat. No. 6,277,375, U.S. Pat. No. 5,869,046, U.S. Pat. No. 5,624,821, U.S. Pat. No. 6,096,871, U.S. Pat. No. 4,479,895, U.S. Pat. No. 6,207,804, U.S. Pat. No. 5,681,566, U.S. Pat. No. 5,864,019, U.S. Pat. No. 5,869,620, U.S. Pat. No. 6,025,165;

U.S. Pat. No. 6,027,725; U.S. Pat. No. 6,239,259; U.S. Pat. No. 6,121,424; WO00/09560; U.S. Pat. No. 6,420,140" [0104]; and

"In addition, those of skill in the art will recognize numerous possible variations of the conjugation methods. For example, the carbohydrate moiety can be used to attach polyethyleneglycol in order to extend the half-life of an intact antibody, or antigen-binding fragment thereof, in blood, lymph, or other extracellular fluids" [0338].

Herman teaches examples of antibody "clearance"

"...(with respect to removing disease associated antibodies from circulation see for example a bispecific dsDNAx monoclonal antibody construct for clearance of anti-dsDNA IgG in systemic lupus erythematosus. J Immunol Methods. 2001 Feb. 1; 248(1-2):125-138). (see also, for example, U.S. Pat. No. 5,968,510 with respect to antibody-CTLA-4 fusion proteins for use in binding to various target ligands)" [0162];

And selecting antibody constructs for the following properties: "avidity, affinity and other elements of design including size, blood clearance additional functionality etc..." [0186].

Slavin-Chiorini teaches measuring serum clearance of the antibodies and half-life measured as RI in the form of tissue localization. Slavin-Chiorini teaches the CH2-domain deleted Mab localizes to tumors earlier and clears from blood faster than the labeled parent Mab (p. 101, Col. 2, ¶2). Slavin-Chiorini teaches:

"Further testing is required to determine the potential clinical utility of the cB72.3ΔCH2 in the light of its lower tumor binding as compared with cB72.3. However, the faster clearance rate, more rapid tumor targeting and lack of metabolic uptake in normal tissues demonstrated with the iodine-labeled CH2 domain-deleted cMAb may be an advantage for certain clinical protocols. For example, an antibody with these characteristics may be useful in instances in which the exposure of normal tissues to a radionuclide conjugated to an MAb needs to be minimized. A cMAb with a faster clearance rate may also be less likely to elicit an immune response in a patient, thereby allowing multiple and/or higher dosages of a cMAb to be administered. The cMAbΔCH2

may also be optimal for conjugation with radioisotopes with shorter half-lives, and allow for the efficient use of the intraoperative gamma-detecting probe or gamma-scanning techniques in patients at an earlier time post-infusion of radiolabeled MAb than is currently possible using intact MAb" (p. 102, Col. 2, ¶3).

The rejection is maintained.

Conclusion

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Primary Examiner
Art Unit 1643